Laryngeal Dysplasia, Squamous Cell Carcinoma, and Variants

Lester D.R. Thompson, MD

KEYWORDS

• Carcinoma, squamous cell • Carcinoma, adenosquamous • Carcinoma, verrucous • Larynx • Dysplasia

Key points

- Dysplasia is now separated into 2 categories: low and high grade.
- Verrucous squamous cell carcinoma is usually a clinicopathologic correlation.
- Basaloid squamous cell carcinoma shows abrupt keratinization and comedonecrosis.
- Up to 30% of Spindle cell squamous cell carcinoma lacks epithelial differentiation by immunohistochemistry.
- Exophytic and papillary squamous cell carcinoma usually have a better prognosis than conventional squamous cell carcinoma.

ABSTRACT

Squamous cell carcinoma (SCC) is a malignant epithelial tumor showing evidence of squamous differentiation. It is the most common malignancy of the larynx, with several variants (verrucous, exophytic or papillary, spindle-cell, basaloid, acantholytic, adenosquamous) recognized, with well-established precursor lesions. Dysplasia is now separated into only low-grade and high-grade categories. Each SCC variant has unique cytomorphologic features and histologic differential diagnoses that are important to consider, as management and outcomes are different.

OVERVIEW

Squamous cell carcinoma (SCC) is a malignant epithelial tumor showing evidence of squamous differentiation and is the single most important and most common malignant neoplasm of the larynx. Although not always present, precursor dysplasia is usually seen.[1] In general, men are affected much more frequently than women, usually in the middle to later decades of life, although any age can be affected.[2,3] Symptoms are nonspecific, with hoarseness, dyspnea, stridor, and dysphagia most common.[4] Independently and synergistically, tobacco (cigarette, cigar, pipe) and alcohol use are the most important risk factors,[5–7] whereas transcriptionally active human papillomavirus (HPV) is less common in laryngeal tumors, detected in up to 15% of cases.[8–10] Genetic predisposition (such as with Lynch syndrome, Bloom syndrome, and Li-Fraumeni, among others), susceptibility (immunologic factors and age), and other environmental and occupational factors probably interact in this multifactorial and multistep process.[11,12] Variants of SCC account for up to 4% of tumors,[13–19] and are separated primarily because they show a different clinical presentation and outcome, as well as frequently raising different differential diagnoses. In the United States, most tumors develop in the glottis, followed by the supraglottis and rarely subglottis, although geographic variation is common. Direct

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Department of Pathology, Southern California Permanente Medical Group, Woodland Hills Medical Center, 5601 De Soto Avenue, Woodland Hills, CA 91367, USA
E-mail address: Lester.D.Thompson@kp.org

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extension into contiguous structures or lymphovascular invasion is common, the latter resulting in a high incidence of regional lymph node metastases. Surgery, laser therapy, and radiation continue to be the mainstays of therapy, with changes in protocols for the specific histologic variants.[20] Outcomes are heavily influenced by tumor stage, localization (glottic), and age,[20–22] whereas differentiation, invasive pattern, vascular and/or perineural invasion, margin status, and extranodal extension play a significant role.[23–33]

DYSPLASIA (PRECURSOR LESIONS)

Dysplasia is defined by a morphologic spectrum of architectural and cytologic changes in the squamous mucosal epithelium that is associated with an increased likelihood of progression to SCC. Gastroesophageal reflux disease is considered a risk factor in addition to tobacco and alcohol use,[34,35] whereas transcriptionally active HPV seems to be of minor importance.[36–38] There are frequent chromosomal changes and loss of heterozygosity, with *CDKN2A* gene alterations most frequently identified, associated with *TP53* and *cyclin-D1* overexpression and activated telomerase activity, but these are not yet clinically useful.[39–41] The vocal cords are affected most frequently, with rare involvement of the commisures.[42]

Leukoplakia, erythroplakia, or mixed leukoerythroplakia appear in the larynx as localized or diffuse patches or flat to exophytic or papillary lesions that mimic SCC. Therefore, histologic evaluation is mandatory for diagnosis.

Over the years, many different grading schemes have been proposed,[43–45] often subject to significant interobserver variability. With a trend in other organs to a 2-grade system,[46,47] generally lesions that are traditionally considered mild dysplasia would be categorized as "low grade" whereas lesions classified as moderate to severe dysplasia/carcinoma in situ can be categorized as "high grade." **Table 1** highlights the architectural and cytomorphological features used to distinguish between low-grade and high-grade dysplasia (as modified from the World Health Organization Classification of Tumours of the Head and Neck). In general, it is a qualitative and quantitative

Table 1
Dysplasia criteria

Low-grade dysplasia (previously mild dysplasia)	Architecture	• Overall stratification is preserved, whereas basal-parabasal layer is abnormal • Basal-parabasal layer is increased, up to lower half of the epithelium • Spinous layer may be increased, with prickle cells usually seen only in upper half of the epithelium
	Cytology	• Limited pleomorphism • Enlarged nuclei with increased nuclear-to-cytoplasmic ratio, but evenly distributed chromatin; vague cytoplasmic pinking with limited intercellular spinous processes • Isolated dyskeratosis cells • Mitoses (typical forms) limited to lower third of epithelium
High-grade dysplasia (previously moderate and severe dysplasia, and carcinoma in situ)	Architecture	• Keratinizing or nonkeratinizing (basal cell) types • Loss of maturation, with disordered stratification and loss of polarity up to full thickness • Cellular pleomorphism from one-half up to full thickness, frequently severe • Basement membrane remains intact (no stromal changes) around irregular-shaped rete (bulbous, downwardly extending)
	Cytology	• Often conspicuous pleomorphism with marked variation in cell and nuclear size and shape, marked variation in staining intensity (often hyperchromatic), and increased size and number of nucleoli • High nuclear-to-cytoplasmic ratio • Dyskeratotic cells increased throughout the epithelium • Increased mitoses anywhere in the epithelial, to include atypical forms (the latter qualifies as high-grade by itself)

Modified from Gale N, Hille J, Jordan R, et al. Tumours of the hypopharynx, larynx, trachea, and parapharyngeal space: precursor lesions. In: El-Naggar AK, Chan JKC, Grandis JR, et al, editors. Pathology and genetics of head and neck tumours. 4th edition. World Health Organization Classification of Tumours. Lyon, France: IARC Press, 2017, in press.